Using Concurrent Cardiovascular Information to Augment Survival Time Data from Orthostatic Tilt Tests

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Orthostatic Intolerance (OI)

Propensity to develop symptoms of fainting during upright standing.

OI is associated with changes in heart rate, blood pressure and other measures of cardiac function.

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Problem: NASA astronauts have shown increased susceptibility to OI on return from space missions.

Current methods for counteracting OI in astronauts include fluid loading and the use of compression garments.

Assessment of OI: Orthostatic Tilt Tests (OTTs)

- Subject initially is supine.
- 80° upright tilt for preset time (T_{max} = 5 - 30 min.)
- "Survival" time = T
- Endpoint: $T_c = \min(T, T_{max})$

Concurrent measurements $\mathbf{x}(t) = [x_1(t),..,x_8(t)]$ ($t <= T_c$):

$x_1(t)$ = heart rate (hr)

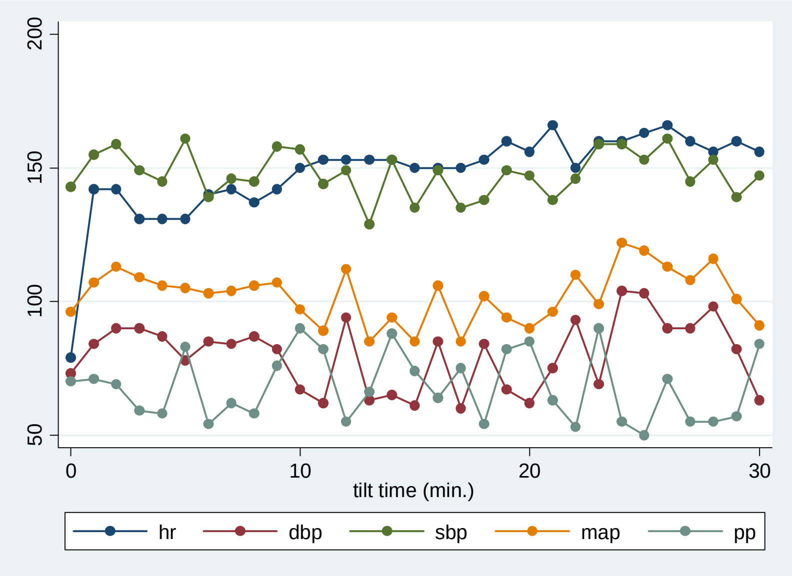
$x_2(t)...x_5(t)$ = measures of blood pressure (dbp, map, sbp, pp)

$x_6(t)$ = stroke volume (sv)

$x_7(t)$ = cardiac output ($co = sv \times hr$)

$x_8(t)$ = total peripheral resistance $tpr = (map - mvp)/co$

Time trajectories of $x_1,\ldots,x_8$ (completed OTT)



x_1 heart rate (*hr*)

x_2 disastolic bp (*dbp*)

x_3 mean arterial bp (*map*)

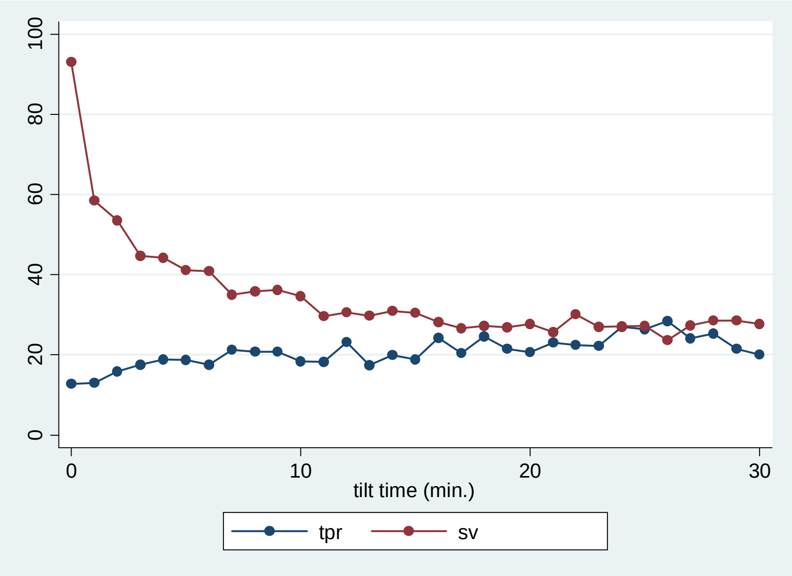
x_4 systolic bp (*sbp*)

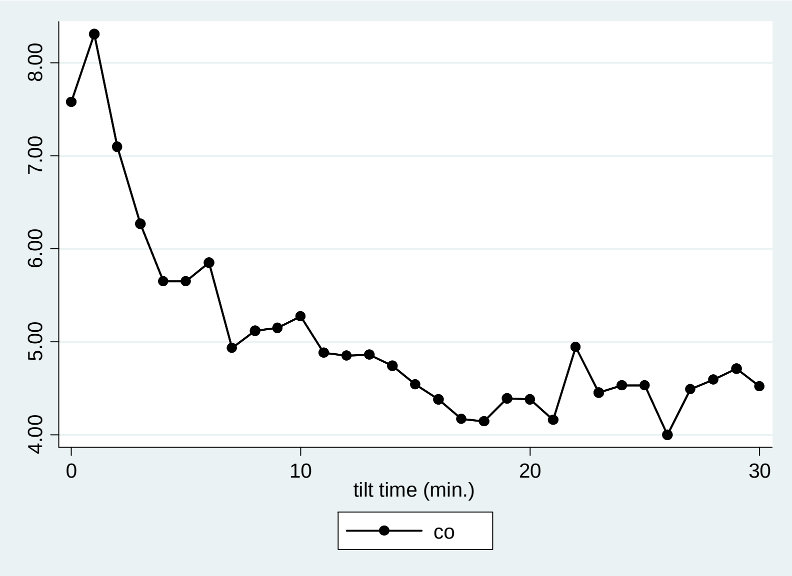
x_5 pulse pressure (*pp*) = *sbp-pp*

x_6 stroke volume (*sv*)

x_7 cardiac output (*co*)

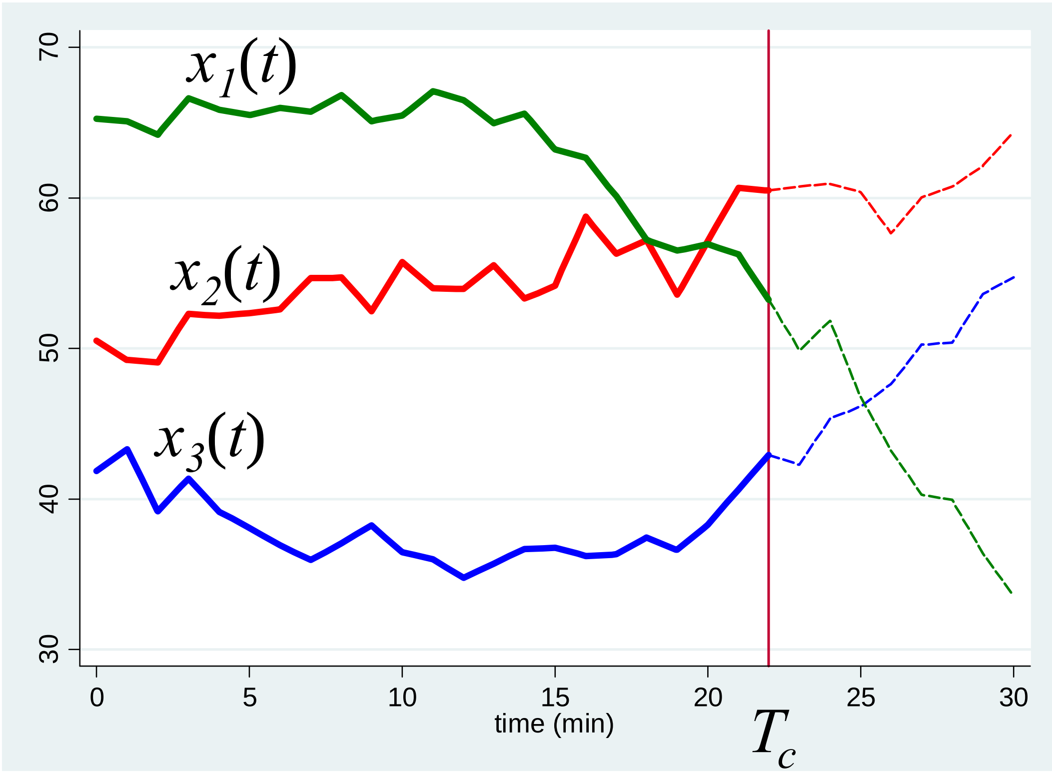
x_8 total peripheral resistance (*tpr*)





Uncompleted OTT

Time trajectories of $\{x_i(t);\, t = 1,..,T_c\}$



Causative Flow (no censoring)

We assume all the information about the degree of OI would be contained in the survival time T, if there were no censoring.

OI $\longrightarrow$ Concurrent measurements $\{\boldsymbol{x}(t); (t \leq T)\}$ $\longrightarrow$ T

Causative Flow (censoring)

With censoring present, both $\{\boldsymbol{x}(t);\ (t \le T_c\ )\}$ and T_c provide information about the survival time T.

$$\mathrm{OI}\ \begin{array}{l} \nearrow\ \{\boldsymbol{x}(t);\ \ (t \le T_c\ )\} \\ \\ \searrow\ T_c = min\ (T,\ T_{max}) \end{array}$$

Bedrest simulation of spaceflight

- 27 subjects (10F, 17M)
- 60-day bedrest
- OTTs pre and post-bedrest
- T_{max} = 30 min.

Endpoint: $T_c = \min(T, T_{max})$ (in min.)

<u>concurrent measurements</u> : ($t = 0, 1, 2, ..., T_c$)
$x_1(t)$ = heart rate (*hr*)
$x_2(t)...x_5(t)$ = measures of blood pressure (*dbp, map, sbp, pp*)
$x_6(t)$ = stroke volume (*sv*)
$x_7(t)$ = cardiac output ($co = sv \times hr$)
$x_8(t)$ = total peripheral resistance $tpr = (map - mvp)/co$

OTT survival times for bedrest subjects, by gender

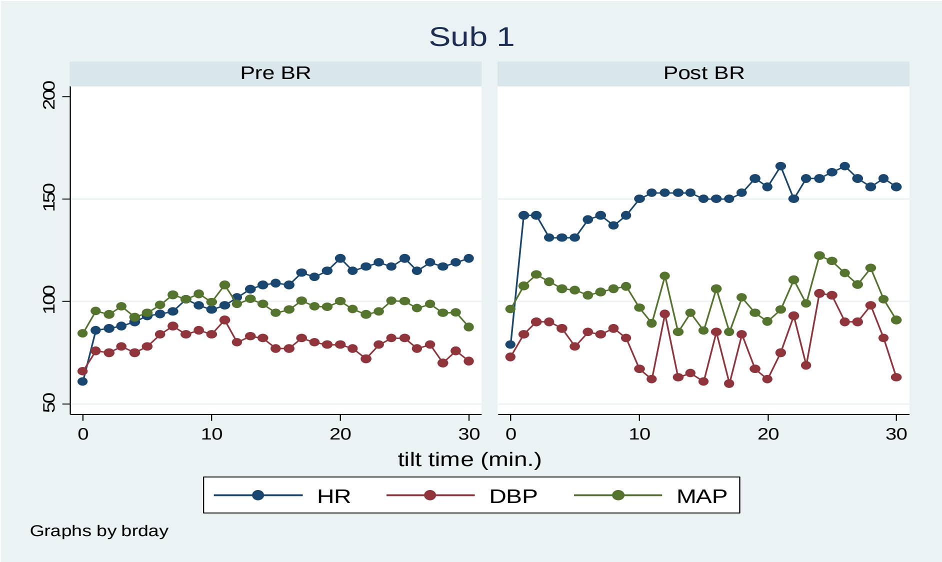
Female

id	pre BR	post BR
4	16	—
8	30	20
9	27	13
10	30	12
11	12	9
15	9	5
17	7	5
18	6	8
21	10	—
22	22	—

Male

id	pre BR	post BR
1	30	30
2	18	8
3	30	22
5	28	24
6	20	—
7	30	—
12	30	—
13	28	—
14	30	—
16	22	11
19	19	29
20	30	3
23	17	6
24	30	1
25	30	9
26	12	3
27	30	26

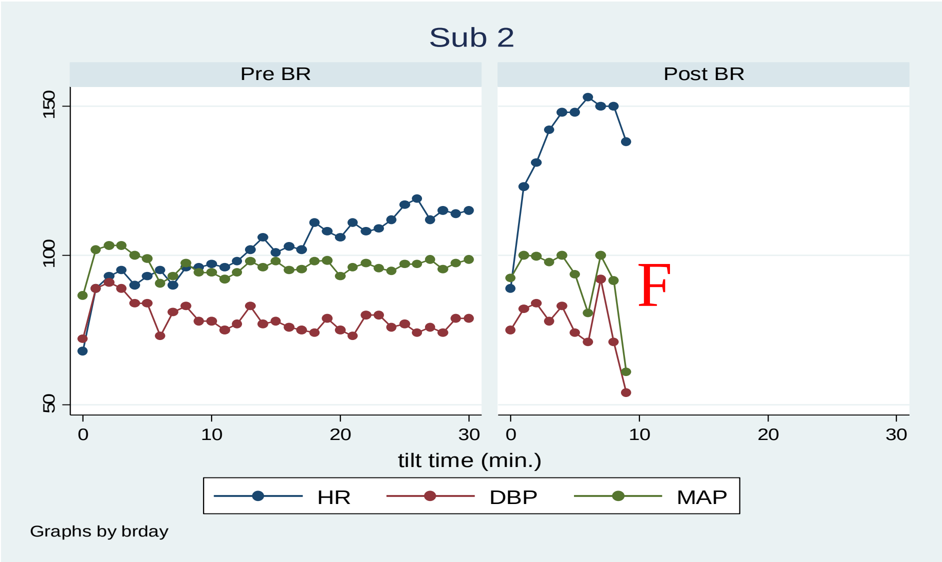
Pre vs. post bedrest comparison (univariate)

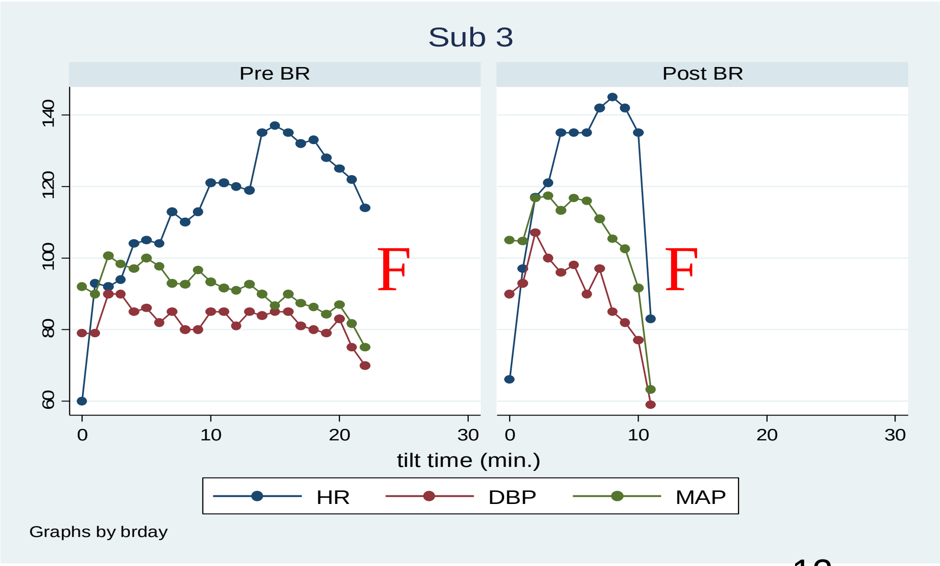


x_1 = heart rate (hr)

x_2 = diastolic blood pressure (dbp)

x_3 = mean arterial pressure (map)

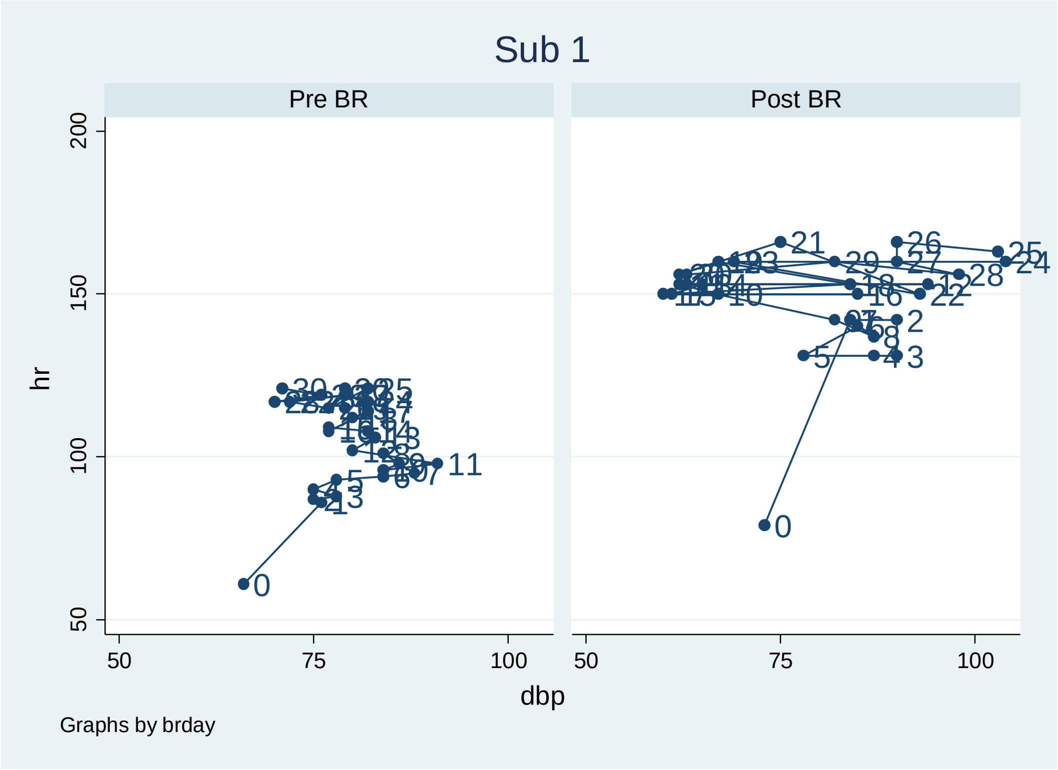




2-d Trajectories

raw values with supine time point

HR

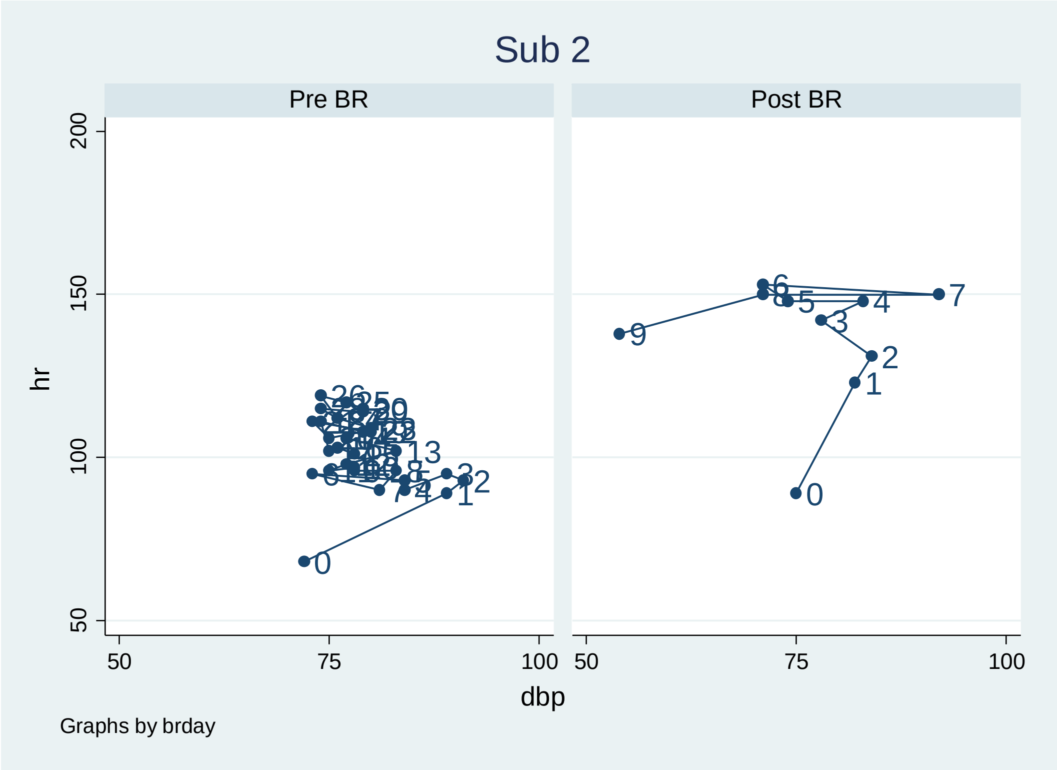


DBP

2-d Trajectories

raw values with supine time point

HR

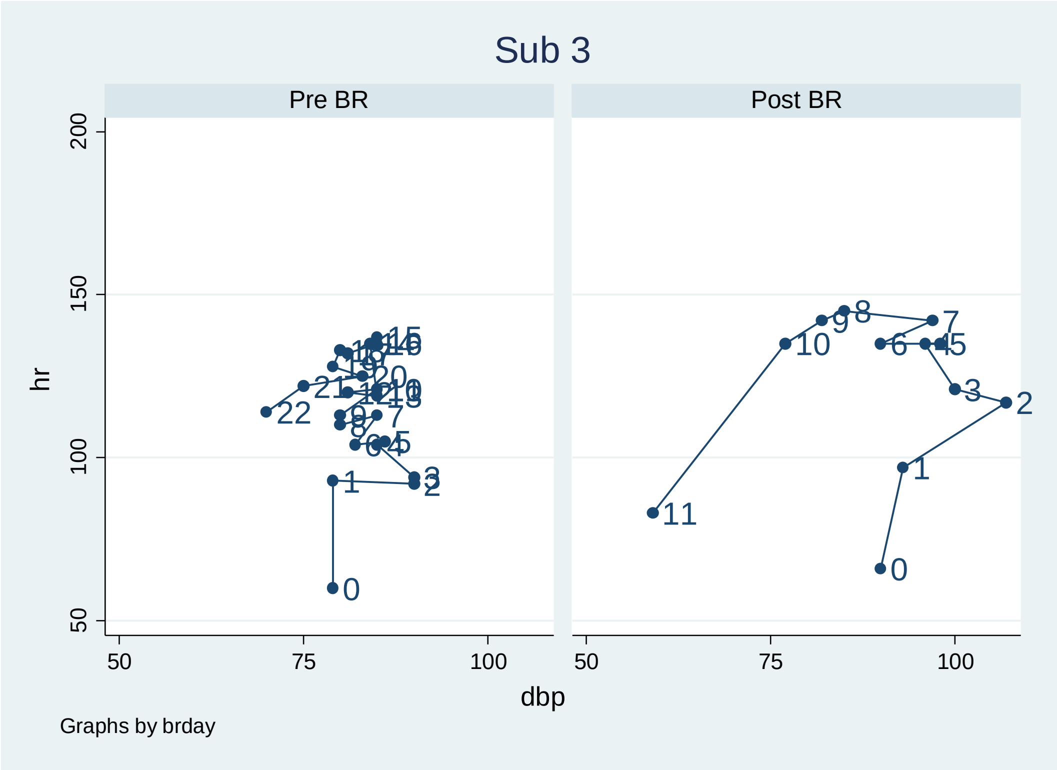


DBP

2-d Trajectories

raw values with supine time point

HR



DBP

Summarizing Behavior of Concurrent Measurements

In practice we seek a summary statistic A that captures the essential information in {x(t)}.

$$\mathrm{OI} \nearrow A = A(\mathbf{x}(t)) \quad (t \le T_c)$$

$$\mathrm{OI} \searrow T_c = min\,(T, T_{max})$$

Desirable properties of A

- Summarizes relevant behavior of $(x_1(t),..,x_8(t))$.
- Can be calculated for OTT of any (reasonable) length.
- A and T_c explain OI better than T_c alone for short tests.

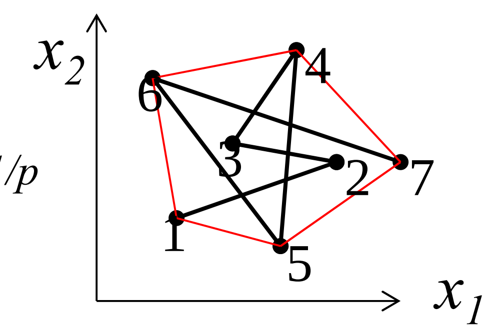
Candidates for $A = A(\boldsymbol{x}(t))$

p-dimensional functional data $\boldsymbol{x}(t)$ is observed at discrete common time points $\{t_1, t_2,..,t_k\}$.

1. determinant: $A_{\mathrm{k}} = |\boldsymbol{S}_k|^{1/p}$; $\boldsymbol{S}_k = \dfrac{1}{k-1}\sum_{i=1}^{k}(\boldsymbol{x}(t_i) - \overline{\boldsymbol{x}}_k)(\boldsymbol{x}(t_i) - \overline{\boldsymbol{x}}_k)'$

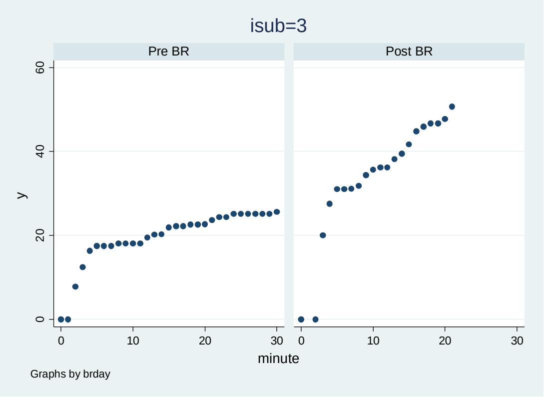
2. path length: $A_k = \sum_{i=1}^{k}|\boldsymbol{x}^*(t_i) - \boldsymbol{x}^*(t_{i-1})|$

3. convex hull area/volume: $A_k = (CHA)^{1/p}$

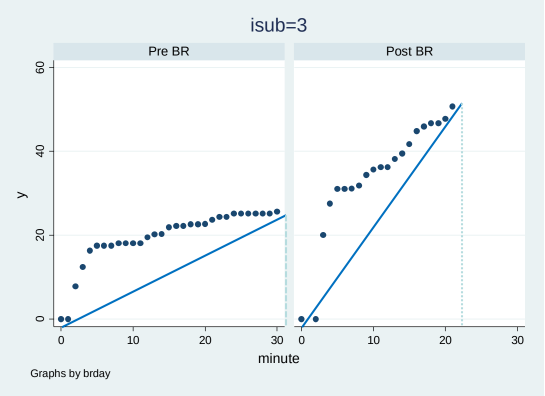


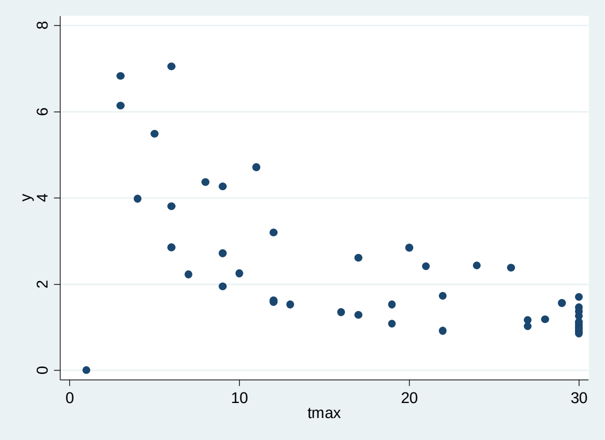
Properties of $A = A(\boldsymbol{x}(t))$

Generally increases with time.



For longer surviving subjects, average slope is lower.





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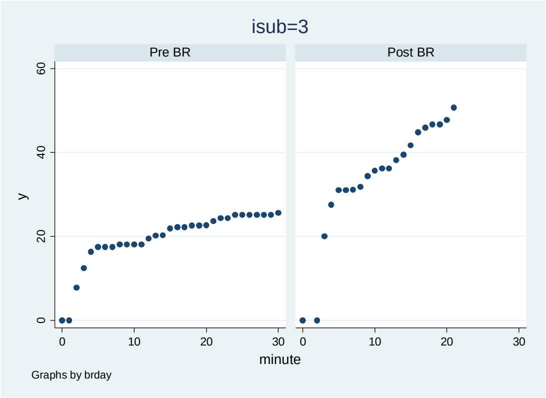

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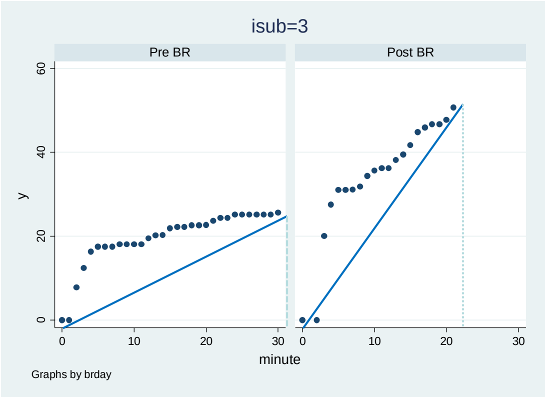
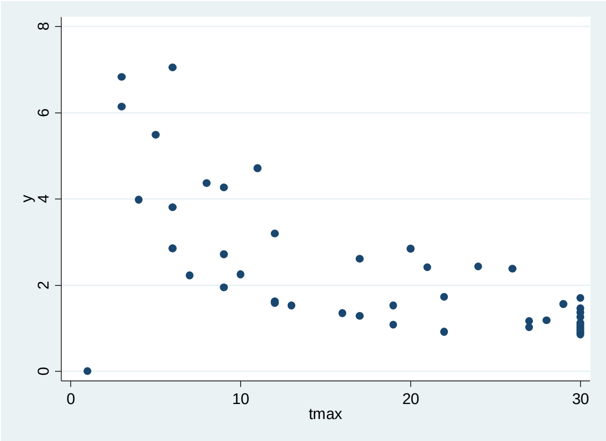




Outcome for inference: $y = A(\mathbf{x}(T_c))/T_c$

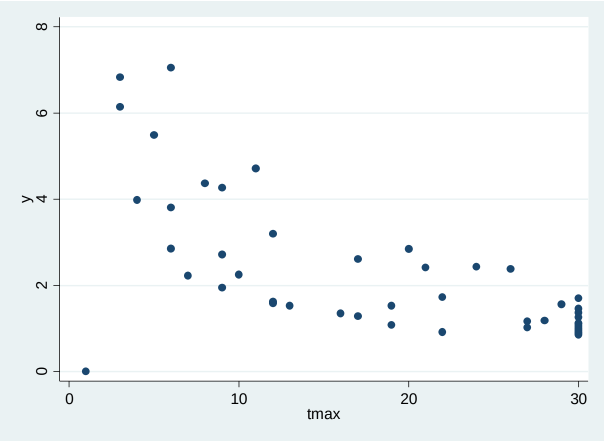
Inference on effect of bed-rest on OI.

$y_{ij} = \mu + u_i + \alpha_j + e_{ij}$ (*i*-th subject; *j*-th treatment)

$T_{ij} \leq T_{max}$ $y_{ij} = A(x(T_{ij}))/T_{ij}$

$T_{ij} > T_{max}$ $y_{ij}\ \varepsilon\ (\ 0, A(x(T_{max}))/T_{max}\ )$

T_{ij} = survival time (may be censored)



Assume y_{ij} ~ Normal
max likelihood (integrate out random effects)

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Exploratory Study Plan

Observe survival and functional data $\boldsymbol{x}(t)$ from OTTs given to subjects pre- and post-bedrest.

Formulate some candidates for $A = A(\boldsymbol{x}(t)) \quad (t \leq T_c))$.

Compare their ability to test for an effect of bedrest at various censoring times with a simple non-parametric analysis.

Contents

Cox regression (OTT survival times)

censoring time: 30 minutes

```
. stcox brday,cluster(isub) nolog

         failure _d:  fail
   analysis time _t:  tmax

Cox regression -- Breslow method for ties

No. of subjects      =           46                Number of obs   =        46
No. of failures      =           34
Time at risk         =          840
                                                   Wald chi2(1)    =     17.03
Log pseudolikelihood =   -108.11632                Prob > chi2     =    0.0000

                                  (Std. Err. adjusted for 27 clusters in isub)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       brday |   3.189786   .8966697     4.13   0.000     1.838583    5.534009
------------------------------------------------------------------------------
```

Cox regression (OTT survival times)

censoring time: 15 minutes

```
. stcox brday,cluster(isub) nolog

         failure _d:  fail15
   analysis time _t:  tmax15

Cox regression -- Breslow method for ties

No. of subjects      =           46                Number of obs   =         46
No. of failures      =           19
Time at risk         =          551
                                                   Wald chi2(1)    =      17.29
Log pseudolikelihood =   -63.369599                Prob > chi2     =     0.0000

                                  (Std. Err. adjusted for 27 clusters in isub)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       brday |    4.66871   1.730109     4.16   0.000     2.258201    9.652309
------------------------------------------------------------------------------
```

Cox regression (OTT survival times)

censoring time: 10 minutes

```
. stcox brday,cluster(isub) nolog

         failure _d:  fail10
   analysis time _t:  tmax10

Cox regression -- Breslow method for ties

No. of subjects      =           46                Number of obs   =        46
No. of failures      =           13
Time at risk         =          406
                                                   Wald chi2(1)    =     13.00
Log pseudolikelihood =   -43.233908                Prob > chi2     =    0.0003

                                  (Std. Err. adjusted for 27 clusters in isub)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       brday |   6.313793   3.227091     3.61   0.000     2.318602    17.19311
------------------------------------------------------------------------------
```

Cox regression (OTT survival times)

censoring time: 7 minutes

```
. stcox brday,cluster(isub) nolog

         failure _d:  fail7
   analysis time _t:  tmax7

Cox regression -- Breslow method for ties

No. of subjects      =           46                Number of obs   =        46
No. of failures      =            8
Time at risk         =          300
                                                   Wald chi2(1)    =      4.98
Log pseudolikelihood =   -25.673825                Prob > chi2     =    0.0257

                                  (Std. Err. adjusted for 27 clusters in isub)
------------------------------------------------------------------------------
             |               Robust
          _t | Haz. Ratio   Std. Err.      z    P>|z|     [95% Conf. Interval]
-------------+----------------------------------------------------------------
       brday |   11.96172    13.3078     2.23   0.026     1.351463    105.8725
------------------------------------------------------------------------------
```

Cox regression (OTT survival times)

censoring time: 5 minutes

```
. stcox brday,cluster(isub) nolog

         failure _d:  fail5
   analysis time _t:  tmax5

Cox regression -- Breslow method for ties

No. of subjects      =           46                Number of obs   =        46
No. of failures      =            4
Time at risk         =          221
------------------------------------------------------------------------------

                                  [no analysis]
```

Best Results
(by Outcome Type and Censoring Time)

cens time	path length	Z	convex hull	Z	determinant	Z
5	HR*, DBP*	4.97	HR	4.71	HR, MAP, SV	3.05
7	HR*, PP*	6.59	HR, DBP, SBP	4.48	HR, DBP, SBP	4.5
10	HR*, TPR*,PP*	7.13	HR, DBP, SBP	6.08	HR, DBP, SBP	5.84
15	HR*, TPR*,PP*	7.58	HR, DBP, SBP	6.67	HR, DBP, SBP	6.05
30	HR*, TPR*,PP*	6.65	HR, DBP, SBP	6.49	HR, DBP, SBP	6.28

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orthostatic tilt testing

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bedrest study

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inference methodology

comparison of variability measures

→ conclusions / remarks

Summary of approach used to developing the statistic $A = A(\mathbf{x}(t));\ t < T_c$

1. Used training data with control condition and provocative condition known to cause OI.

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4. Used simple non-parametric test that combines survival data with cumulative evaluations of each A-candidate to make inference on the effect of condition.

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3. Formulated several measures of this variability as candidates for A.
4. Used simple non-parametric test that combines survival data with cumulative evaluations of each A-candidate to make inference on the effect of condition.
5. Compared results.

conclusions / remarks

Multivariate trajectory spread is greater as OI increases.

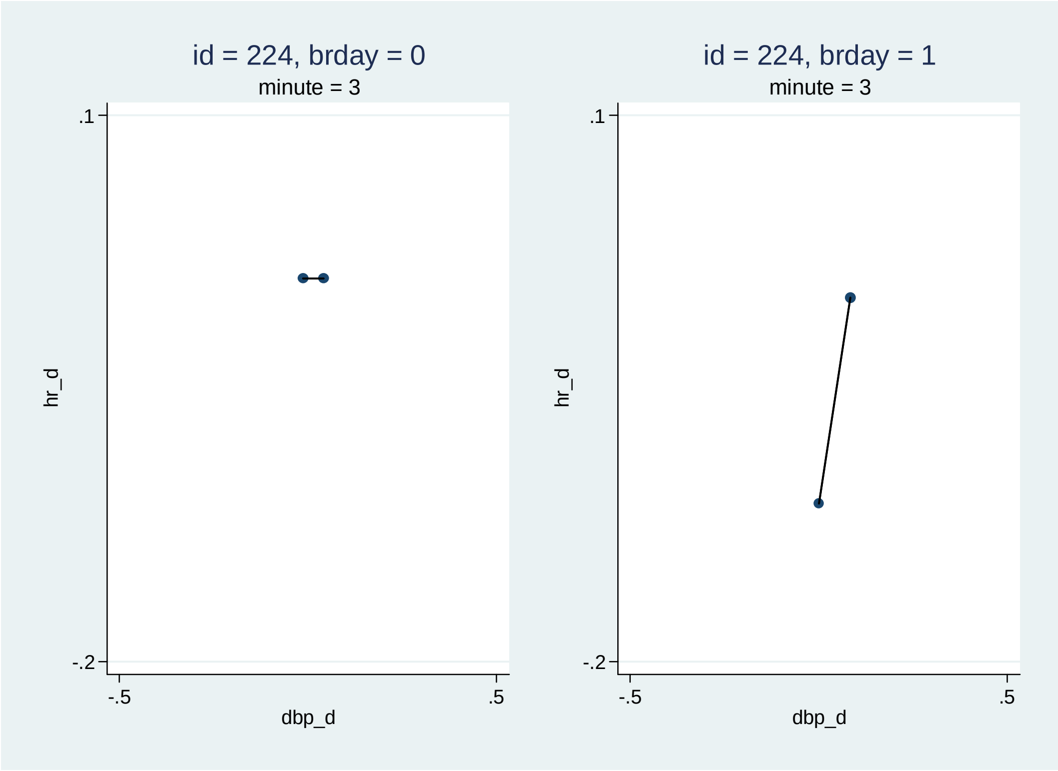
Pairwise comparisons at the same time within subjects allows incorporation of pass/fail outcomes.

Path length, convex hull area, and covariance matrix determinant do well as statistics to summarize this spread

Missing data problems

Time series analysis

- need many more time points per OTT session
- treatment of trend?
- how incorporate survival information?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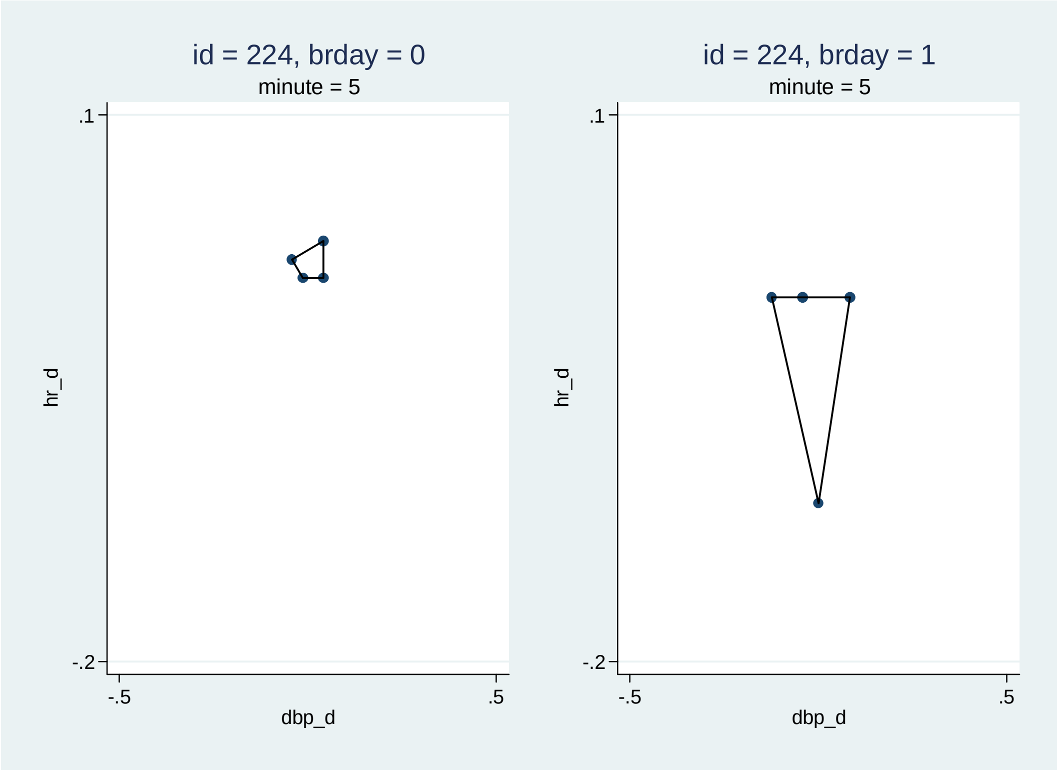
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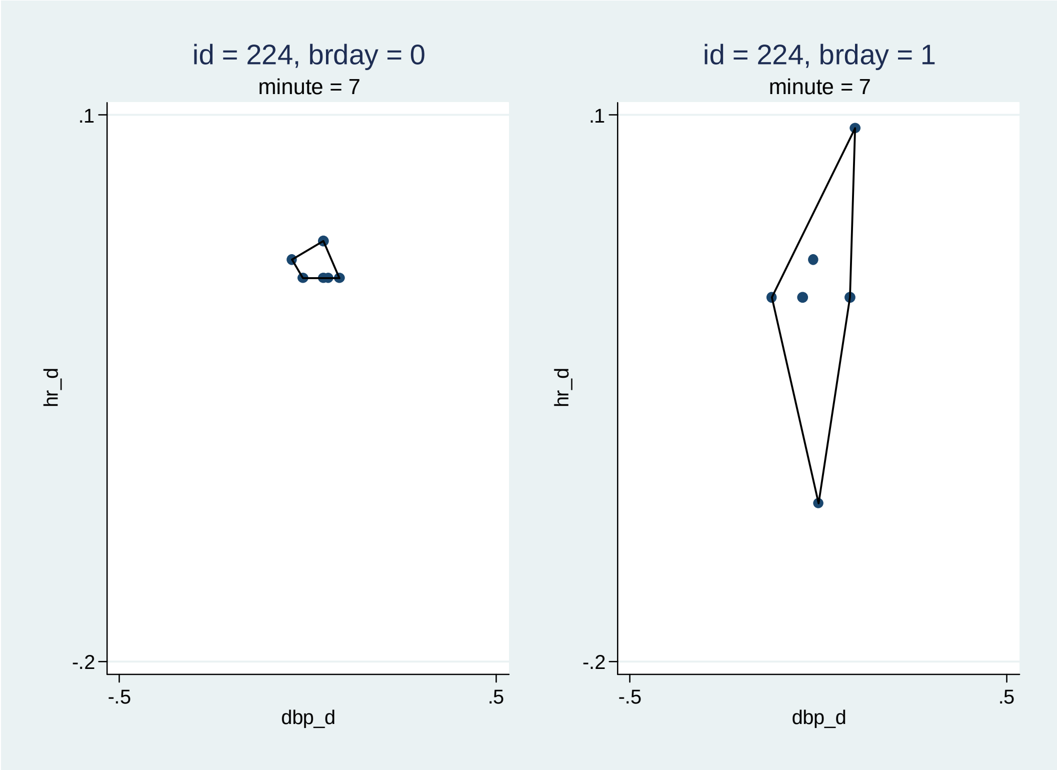

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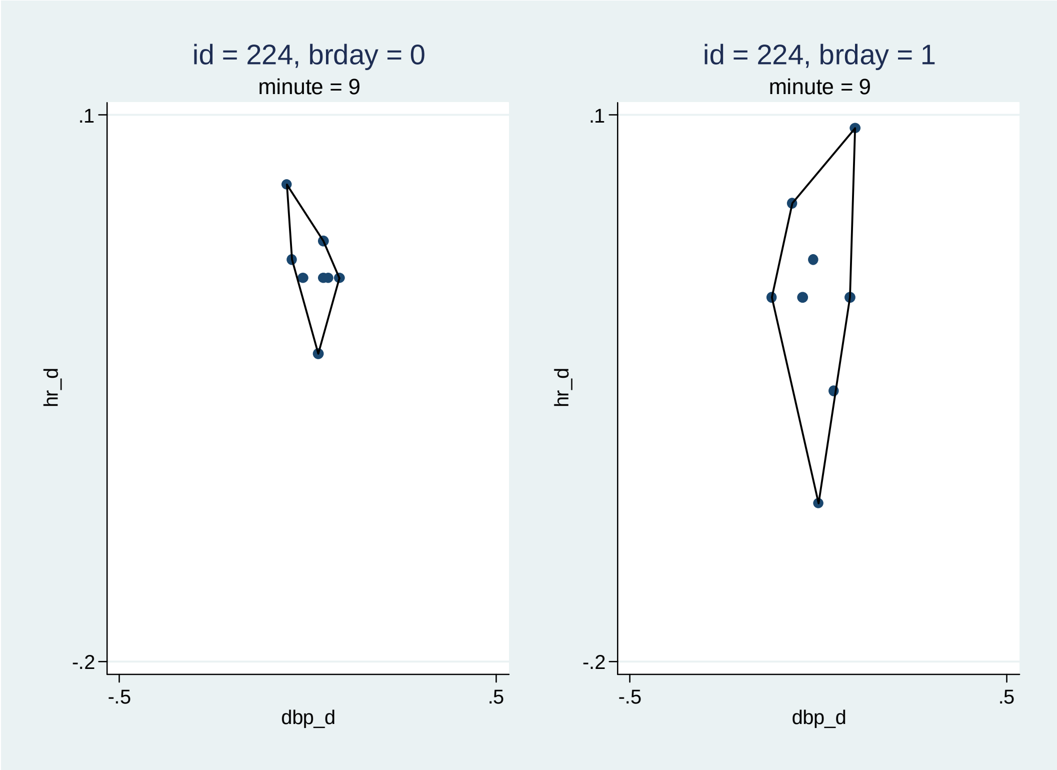
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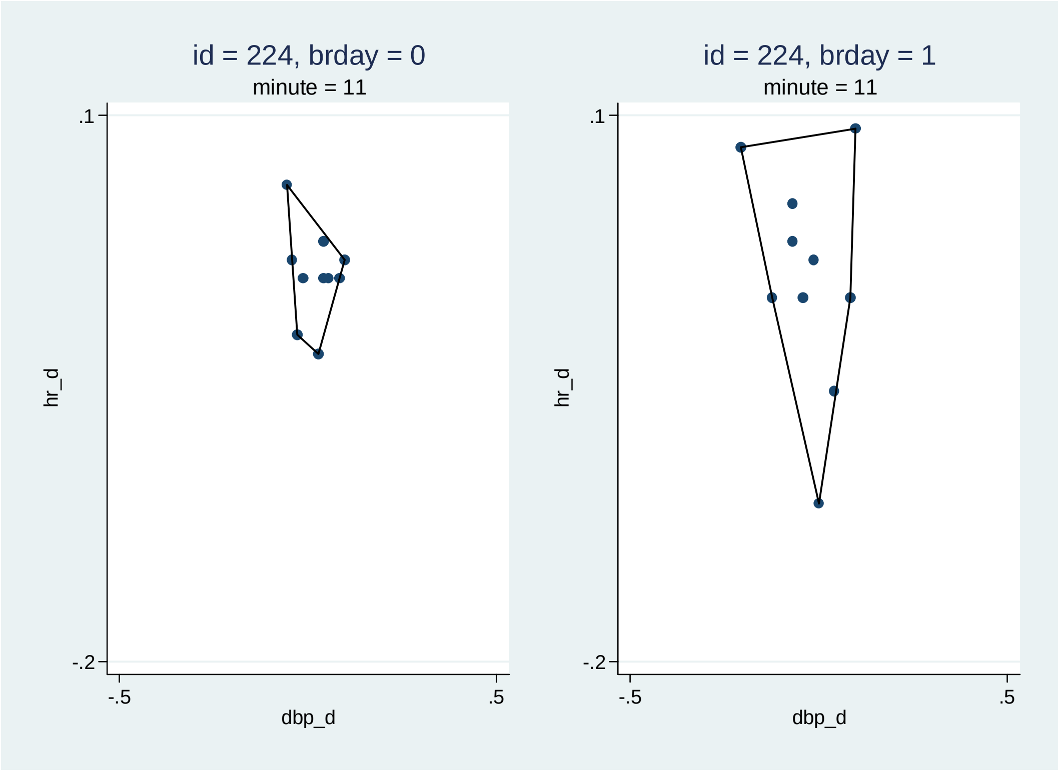

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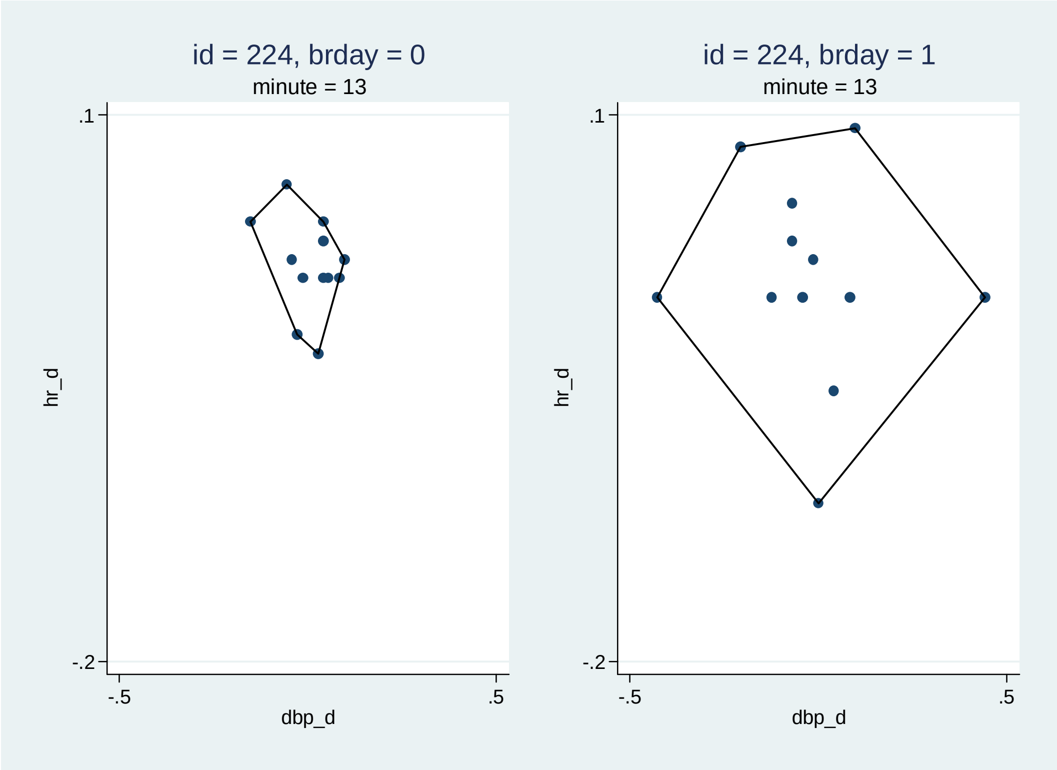
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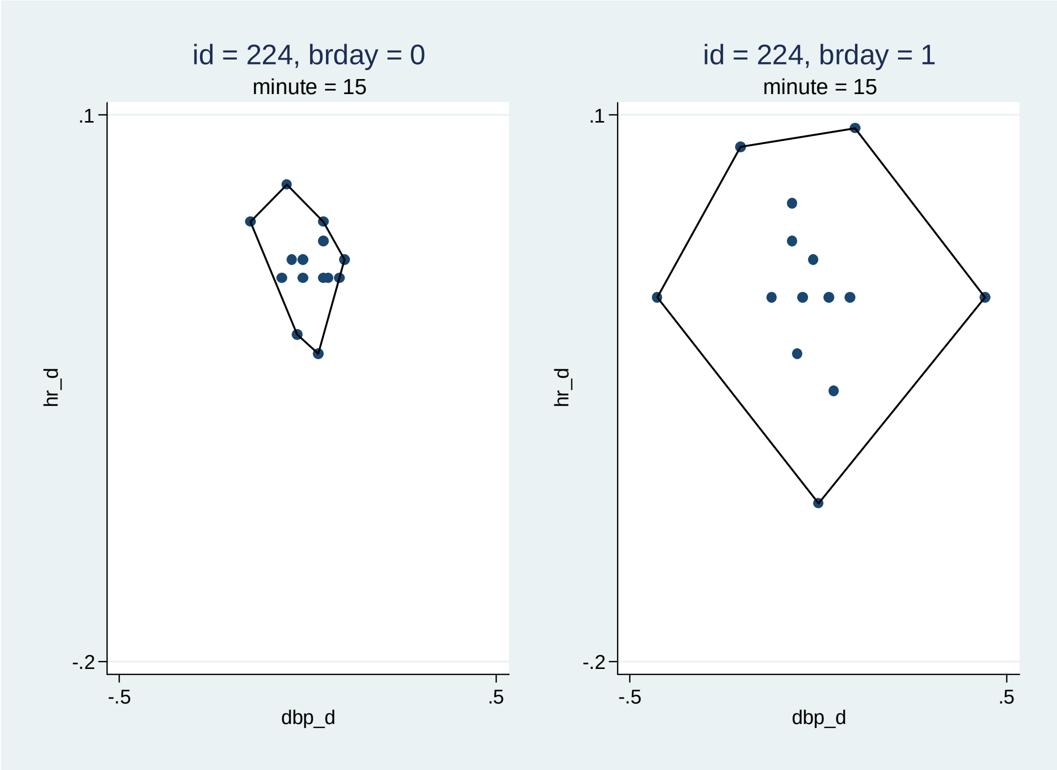
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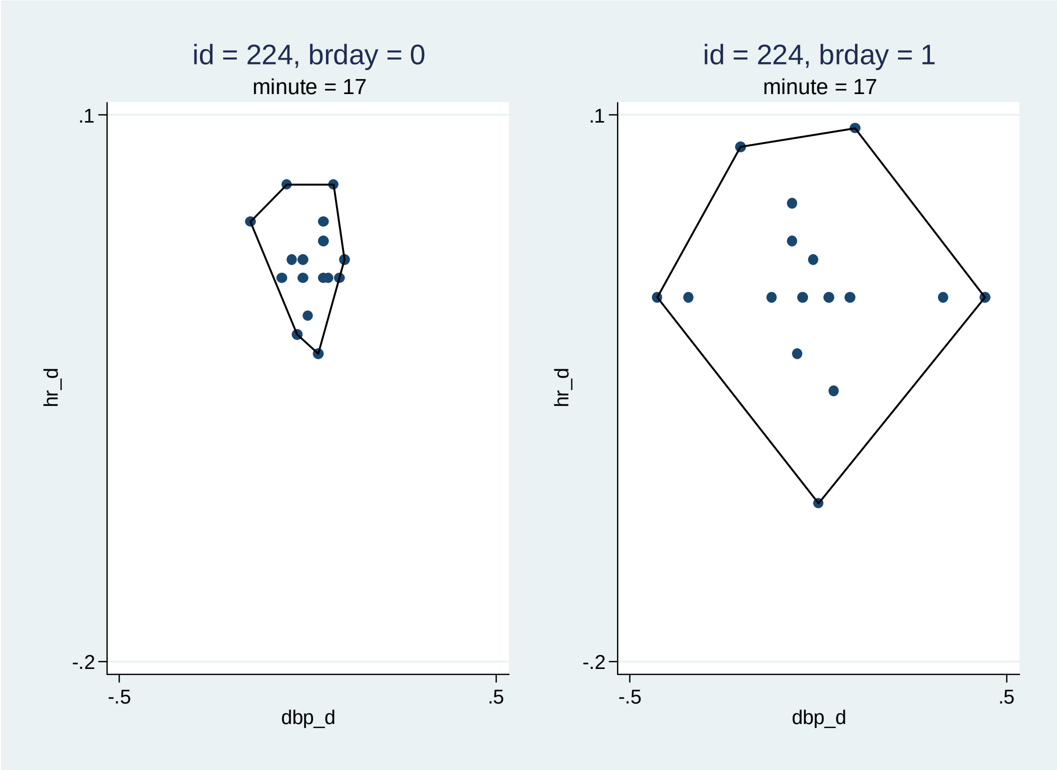

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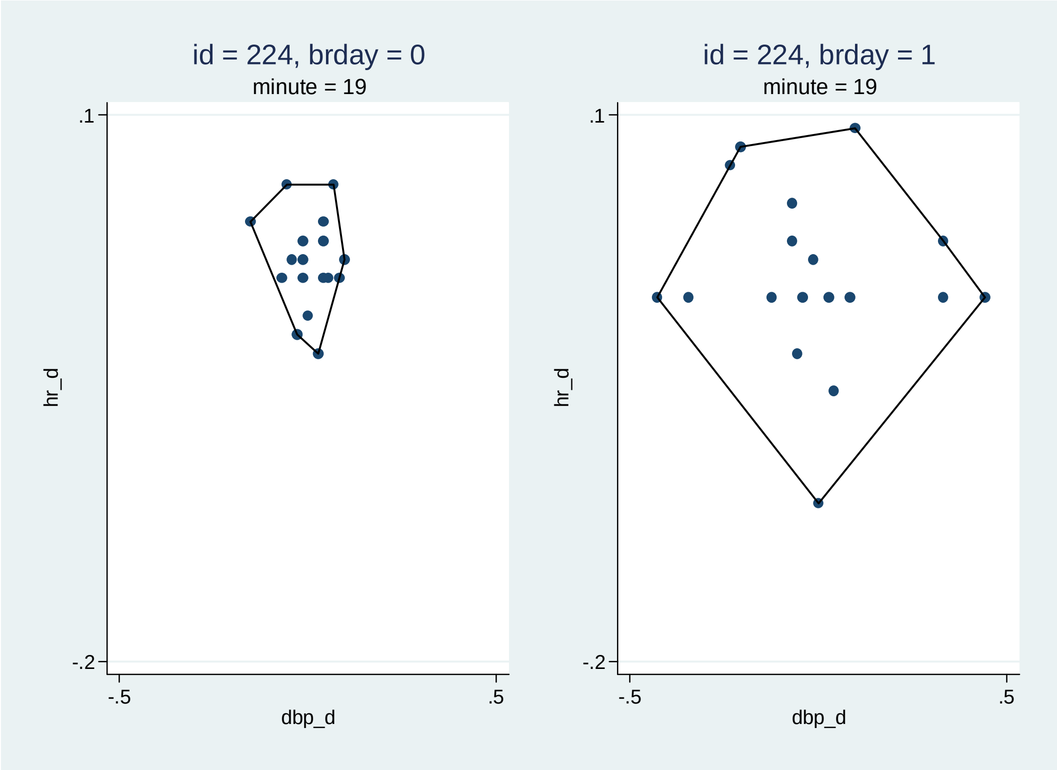
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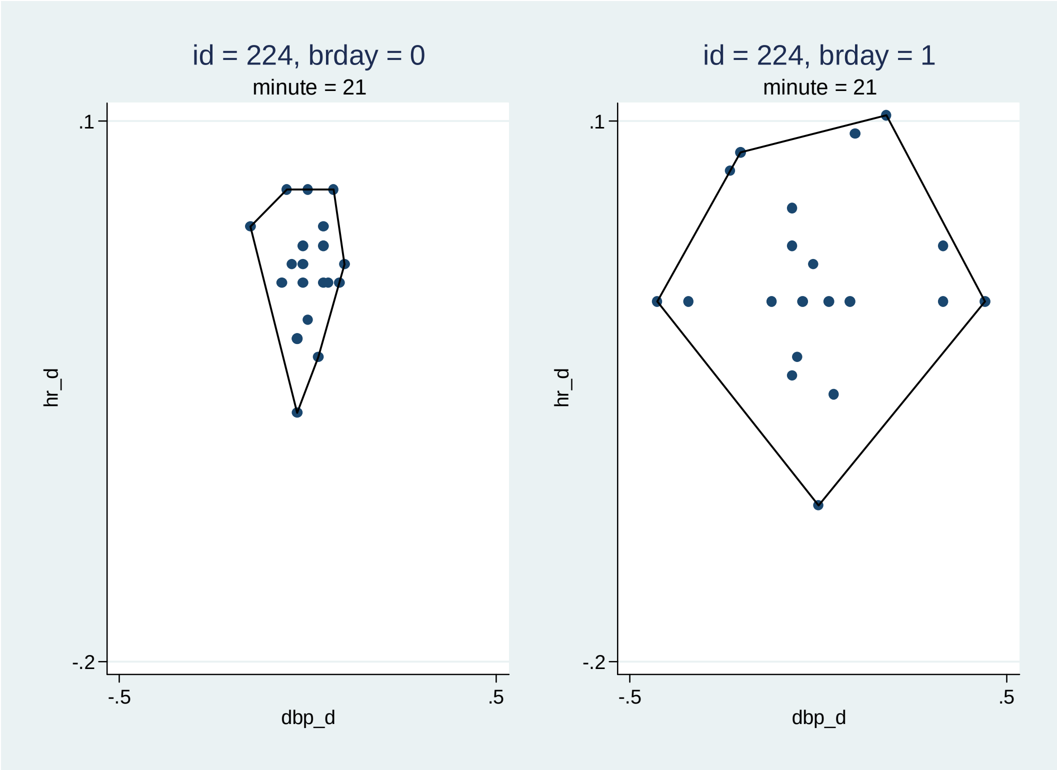
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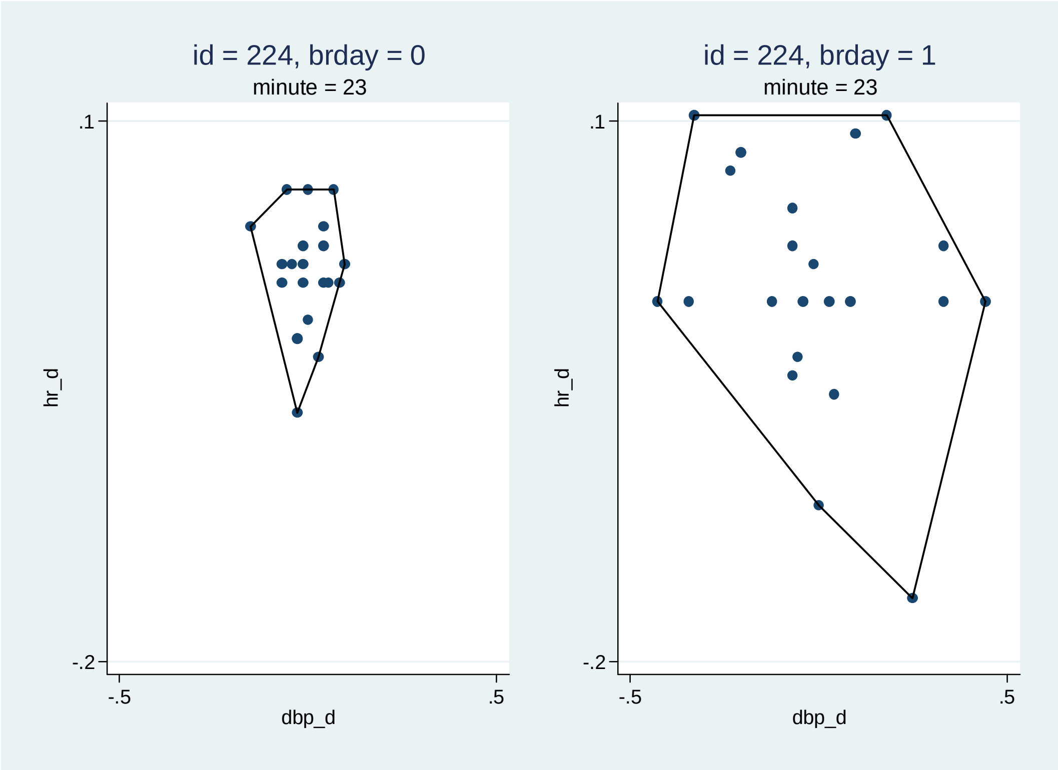
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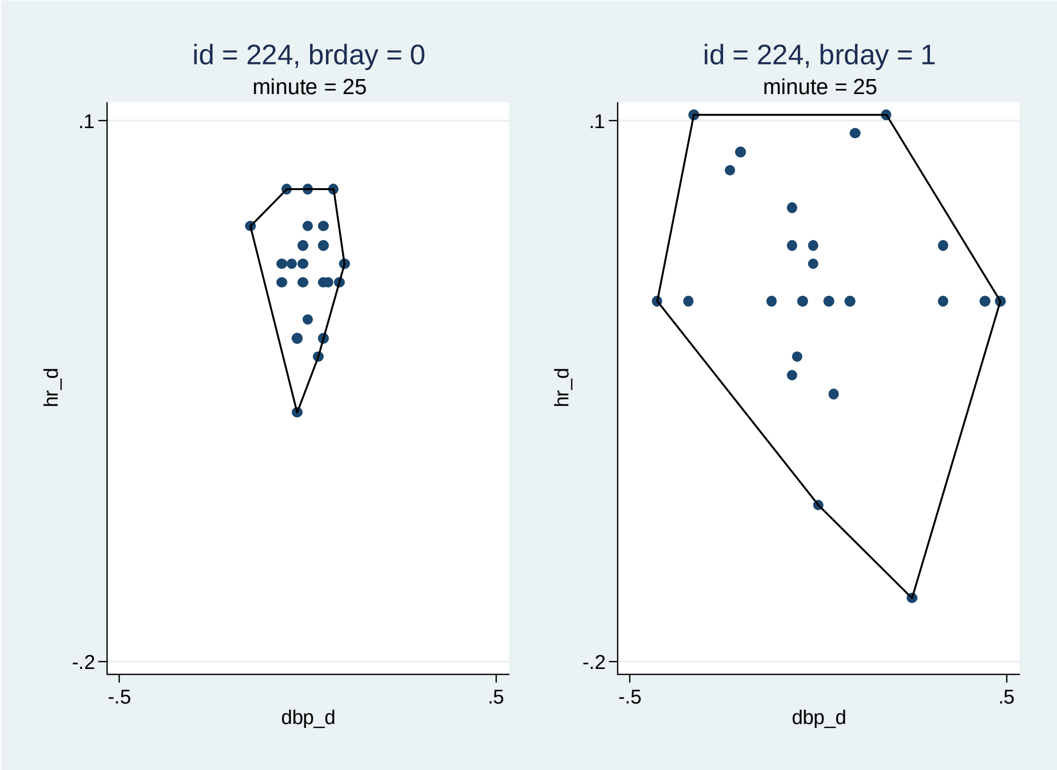

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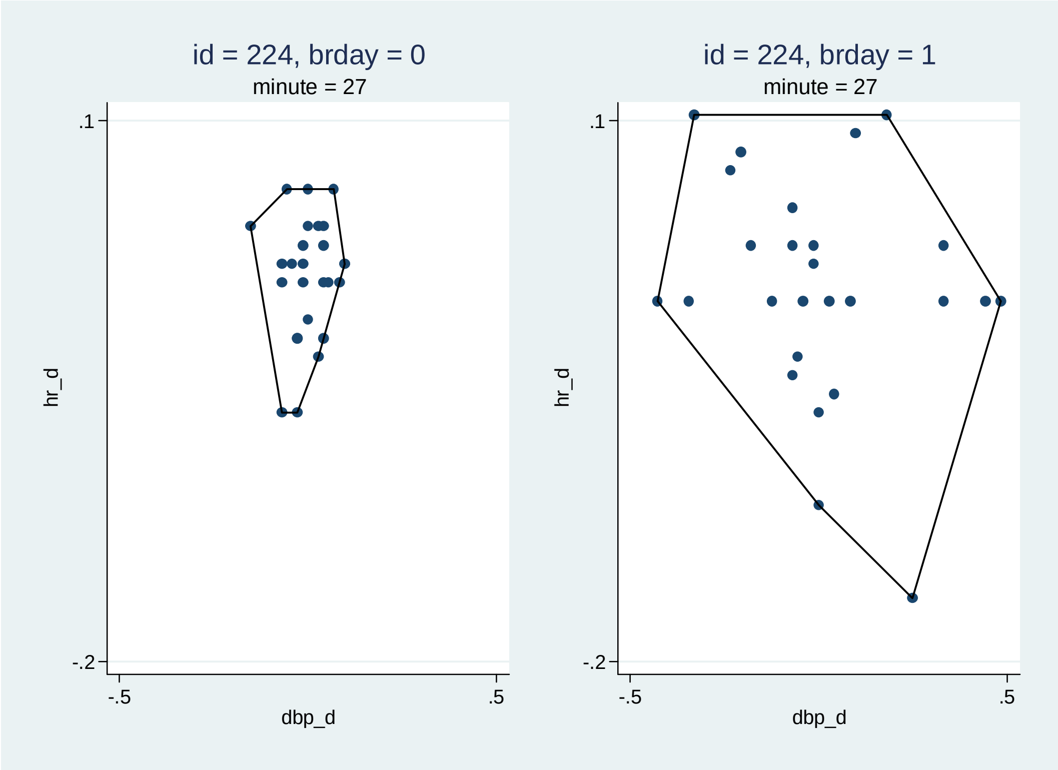
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minute = 27
.1
-.2
hr_d
-.5
.5
dbp_d
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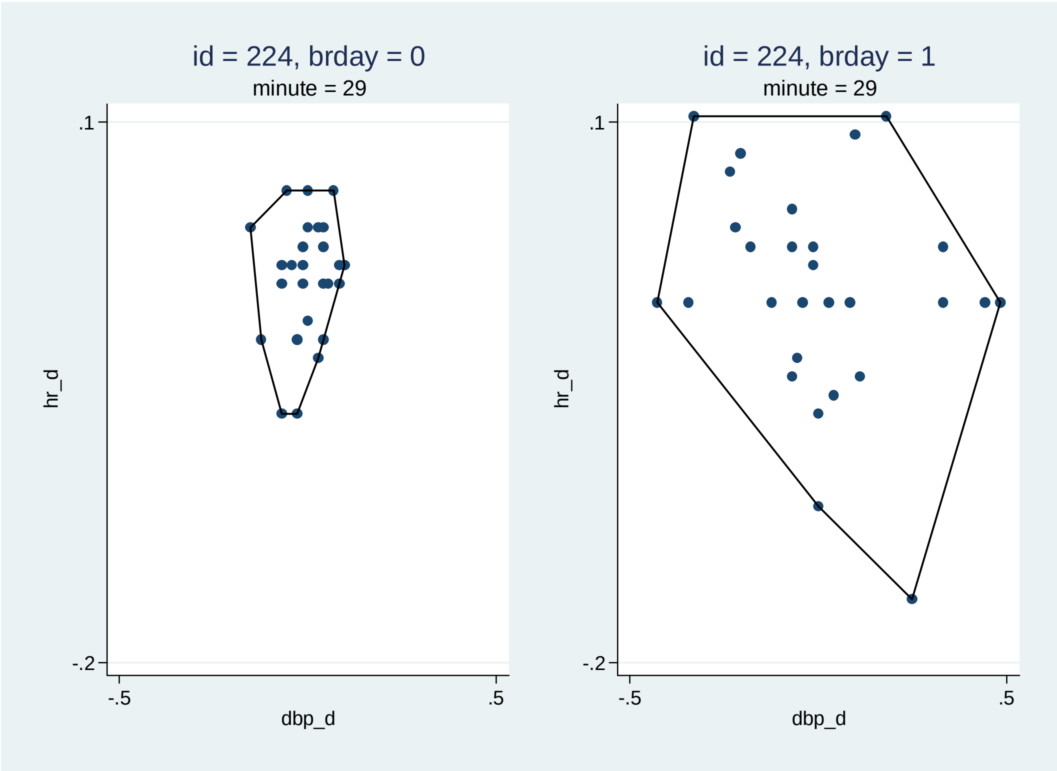
minute = 27
.1
-.2
hr_d
-.5
.5
dbp_d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minute = 29
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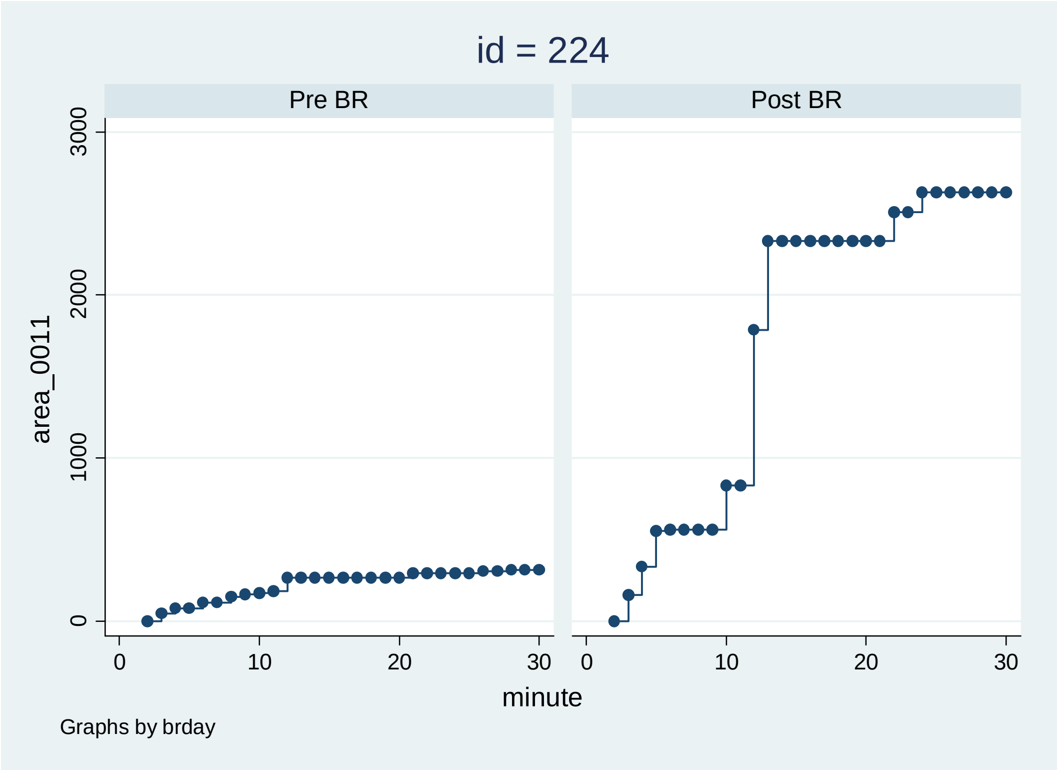
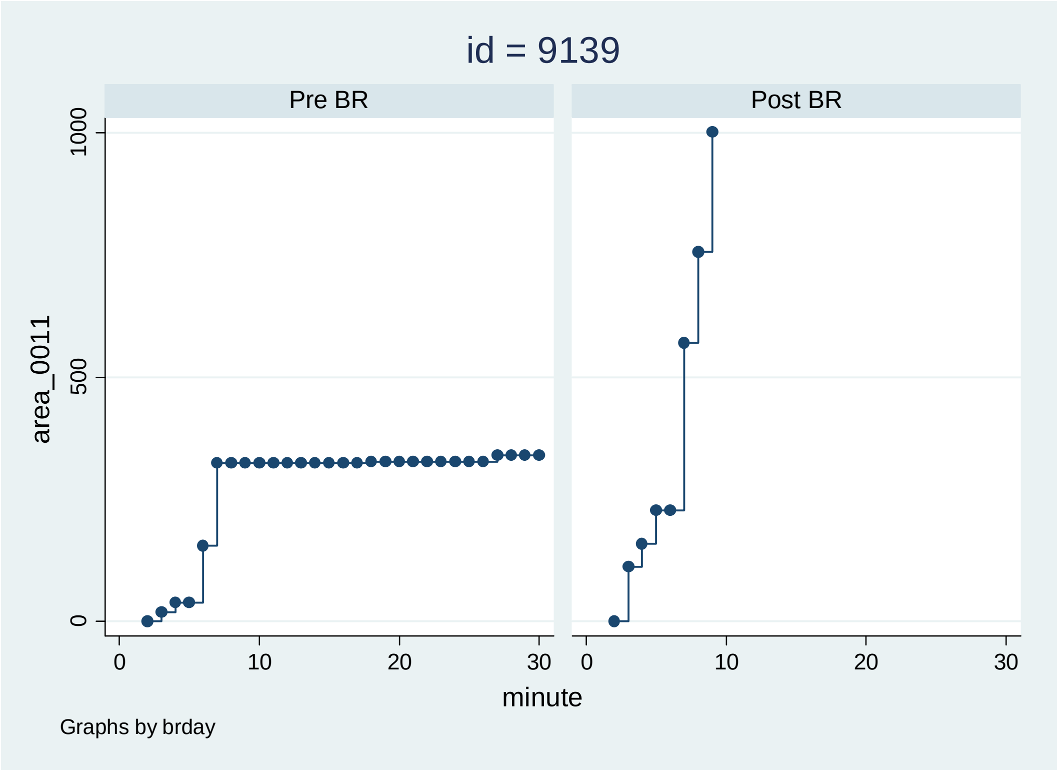
-.2
hr_d
-.5
.5
dbp_d
id = 224, brday = 1
minute = 29
.1
-.2
hr_d
-.5
.5
dbp_d


id = 224
Pre BR
Post BR
area_0011
0
1000
2000
3000
0
10
20
30
minute
Graphs by brday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Pre BR
Post BR
area_0011
0
500
1000
0
10
20
30
0
10
20
30
minute
Graphs by brday